DYNAMICS DAYS SOUTH AMERICA 2010
International Conference on Chaos and Nonlinear Dynamics

**INPE – National Institute for Space Research**
**São José dos Campos – SP – Brazil – July 26-30, 2010**

# GENERIC DYNAMIC MODELING OF METABOLIC SYSTEMS

*Delali A. Adiamah, Julia Handl, Jean-Marc Schwartz*

Faculty of Life Sciences, University of Manchester, Manchester, M13 9PT, UK; jean-marc.schwartz@manchester.ac.uk

**Keywords**: Dynamics of Biosystems; Complex Networks; Metabolism.

## 1. BACKGROUND

The field of systems biology aims to examine the dynamic properties of biological processes as a whole rather than in isolated components. Biological phenotypes typically arise from complex sets of interacting biochemical processes whose effects are difficult to predict from qualitative observation and reductionist analysis. As a consequence, recent years have witnessed a rapid development in the construction of quantitative, predictive mathematical models describing the interactions between intracellular biochemical compounds.

Progress has been particularly widespread in the area of cellular metabolism. Metabolic networks describe the set of biochemical reactions through which living organisms transform nutrients into energy and biomass allowing them to maintain their structure, grow and reproduce. These networks typically contain from a few hundred to a few thousand of reactions. Stoichiometric models, which embed the topology of metabolic reactions and the mass conservation property, have been built at the scale of entire organisms for many species from microorganisms to humans. However, these models provide limited insights into the functioning of cellular processes since their use is limited to steady-state simulations. To understand the detailed dynamics of cellular functions and their regulation, it is necessary to advance toward dynamic models where the behavior of the system can change over time.

To construct a dynamic model of the metabolism of an entire cell is highly challenging since it requires the assembly and solving of systems of several hundred of non-linear differential equations. Furthermore, the kinetic rate equations of individual reactions are often complex and poorly known. Parameter values need to be measured by expensive and time-consuming experiments, and values available in the literature may vary depending on specific *in vitro* or *in vivo* experimental conditions. Therefore, a degree of generalization and simplification is required to reduce model complexity and streamline model construction.

Nevertheless, there is growing awareness that exact rate equations and precise parameters values are often not crucial in determining the fundamental dynamic properties of biological systems. Studies have shown that the main phenotypes of many biological systems are insensitive to changes in parameter values inside a large space of variations, except for a few combinations of key parameters [1]. Biological systems are by nature robust and resilient to perturbations since living organisms must maintain homeostasis of their intracellular functions despite fluctuating environmental conditions. The predictive and informative value of models is thus not necessarily or wholly dependent on a high level of detail in the modeling of individual processes.

## 2. GENERIC KINETIC EQUATIONS

Building on these principles, we developed a modeling framework based on generic kinetic equations in order to enable the construction of large dynamic models of metabolic systems and reach the necessary scale for cell-wide simulations. A widely used formulation of metabolic reaction kinetics is the Michaelis-Menten rate equation, which relies on a two-step scheme describing the binding of a catalytic enzyme to the reaction substrate and subsequent release of the reaction product. For a simple reversible reaction transforming a substrate S into a product P, the reaction rate $v$ is given by

$$v = \frac{e_0\left(\frac{v_+^m s}{K_{mS}} - \frac{v_-^m p}{K_{mP}}\right)}{1 + \frac{s}{K_{mS}} + \frac{p}{K_{mP}}} \qquad (1)$$

where $e_0$ is the concentration of enzyme, $s$ and $p$ are the concentrations of S and P respectively, $v_+^m$ and $v_-^m$ are the limiting rates of the forward and backward reaction respectively, $K_{mS}$ and $K_{mP}$ are the Michaelis constants associated to S and P respectively.

Variants of equation (1) were derived for reactions involving multiple substrates and products, reversible and irreversible reactions, and different catalytic mechanisms, using the King-Altman method [2]. These equations offer a reliable approximation of the kinetics obeyed by most real enzyme-catalytic reactions. Under the further assumptions that biochemical reactions are reversible and that interactions between metabolic compounds and enzymes play a negligible role, it becomes possible to automate the generation of kinetic equations for large systems of metabolic reactions using only the topology

and stoichiometry of the metabolic network.

## 3. GENERIC MODEL OF YEAST GLYCOLYSIS

### *3.1. Model construction*

We applied these principles to construct a generic model of the glycolysis pathway of the baker's yeast *Saccharomyces cerevisiae* and compared its properties to a model based on the experimental determination of rate equations and parameters developed by Teusink *et al.* [3]. Glycolysis is a major metabolic pathway describing the conversion of glucose into pyruvate, which occurs in nearly all organisms. It is also one of the best experimentally characterized, making it an ideal case study to assess whether the behavior of a metabolic system can be predicted without accurately measuring the rate equations and detailed kinetics of every enzyme.

Our model includes all enzymes involved in the pathway from glucose uptake to the production of pyruvate and ethanol. All reactions were assumed to be reversible and of a random-order mechanism. The initial concentrations of metabolites were the same as in the Teusink model. Generic rate equations were derived from the stoichiometry of the network and assembled into a system of ordinary differential equations. The model parameters were estimated from steady-state simulations by the Teusink model with glucose uptake concentrations of 10 and 50 mM.

### *3.2. Simulations and model validation*

We first verified whether the generic model correctly reproduced the behavior of the glycolytic system at steady state, without any perturbation, when glucose uptake was at 10 and 50 mM. We obtained a near-perfect agreement between our model and the Teusink model, confirming that the model reproduced the correct concentration and flux values used in the training data (Table 1).

We subsequently simulated the effect of a dynamically reduced uptake of glucose: after 30 min, the concentration of glucose was reduced from the original 50 to 10 mM. Results from this experiment again showed an excellent agreement between our model and the Teusink model with the same reduction in glucose uptake.

**Table 1 – Selected concentrations and fluxes in simulations by the generic glycolysis model and the Teusink model [4].**
G6P: glucose 6-phosphate; F6P: fructose 6-phosphate; PYR: pyruvate; HK: hexokinase; PGI: glucose 6-phosphate isomerase; PGK: phosphoglycerate kinase.

| Metabolite concentrations (mM) | Glucose 10 mM | Glucose 100 mM | Fluxes (mmol $min^{-1}$ $l^{-1}$) | Glucose 10 mM | Glucose 100 mM |
|---|---|---|---|---|---|
| Generic model | | | | | |
| G6P | 0.73 | 1.07 | HK | 80.13 | 89.48 |
| F6P | 0.07 | 0.11 | PGI | 69.39 | 78.58 |
| PYR | 6.73 | 8.80 | PGK | 121.59 | 138.49 |
| Teusink model | | | | | |
| G6P | 0.72 | 1.09 | HK | 80.16 | 89.25 |
| F6P | 0.07 | 0.12 | PGI | 69.36 | 78.45 |
| PYR | 6.72 | 8.85 | PGK | 121.48 | 138.57 |

Additional simulations were carried out to verify if the model would predict new states of the glycolysis pathway outside the range of training data and without re-estimating the kinetic parameters. We carried out simulations by changing the level of glucose to 1, 100 and 200 mM and the results again showed an excellent agreement between our generic model and the Teusink model (Table 1). Moreover, the generic model appeared to be more robust since it was still able to produce results with very low concentrations of glucose (1 mM) while the Teusink model was unsuccessful when glucose uptake was lower than 2 mM.

### *3.3. Elementary modes analysis*

In order to test our underlying hypothesis that metabolic systems are resilient to perturbation, we further analyzed the distribution of elementary mode fluxes in the generic model over a wide range of parameter values. In metabolic systems, elementary modes are minimal feasible steady-state routes corresponding to elementary paths of biochemical transformations between metabolites. Elementary modes constitute a basis of metabolic functions; every steady-state flux distribution can be decomposed into elementary mode fluxes [4]. This analysis revealed that one elementary mode remains dominant in all cases while other modes generally carry low flux. The glycolysis system therefore exhibits stable behavior upon perturbations and only reaches a small subset of the space of stoichiometrically feasible states.

## 4. CONCLUSION

Through the example of the yeast glycolysis system, we showed that a model based on generic kinetic equations is able to simulate a metabolic system with a comparable accuracy to a detailed model based on detailed experimental determinations. We implemented this methodology in the GRaPe software [5]. These principles may be exploited to automate the construction of large models of intracellular metabolism and achieve the scales needed for cell-wide dynamic modeling.

## References


[1] R.N. Gutenkunst, J.J. Waterfall, F.P. Casey, K.S. Brown, C.R. Myers, J.P. Sethna, "Universally sloppy parameter sensitivities in systems biology models", PLoS Comput. Biol., Vol. 3, No. 10, pp. 1871-1878, October 2007.

[2] A. Cornish-Bowden, "Fundamentals of Enzyme Kinetics", Portland Press, London, 3rd Edition, 2004.

[3] B. Teusink, et al., "Can yeast glycolysis be understood in terms of in vitro kinetics of the constituent enzymes? Testing biochemistry", Eur. J. Biochem., Vol. 267, No. 17, pp. 5313-5329, September 2000.

[4] J.M. Schwartz, M. Kanehisa, "A quadratic programming approach for decomposing steady-state metabolic flux distributions onto elementary modes", Bioinformatics, Vol. 21, Suppl. 2, pp. ii204-205, September 2005.

[5] D.A. Adiamah, J. Handl, J.M. Schwartz, "Streamlining the construction of large-scale dynamic models using generic kinetic equations", to appear in Bioinformatics, 2010.